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EXAMINER

LANDAU, SHARMILA GOLLAMUDI

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte CARLOS PICORNELL DARDER

Appeal 2009-001922¹
Application 09/491,624
Technology Center 1600

Decided: September 4, 2009

Before DEMETRA J. MILLS, ERIC GRIMES, and
RICHARD M. LEOVITZ, *Administrative Patent Judges*.

LEOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

¹ Heard July 8, 2009.

This is a decision on the Patent Applicant's appeal from the Patent Examiner's rejection of claims 15, 16, 18-25, 30, 31, 33, 34, 36, and 39-50. Jurisdiction for this appeal is under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The claims are directed to methods for making an oral pharmaceutical preparation comprising a benzimidazole compound which is coated on an inert nucleus and covered with an enteric coating (Spec. 7:6-7). The oral formulation is an anti-ulcer drug (*id.*). The formulation is prepared in fluid bed coater of the "Wurster" type (*id.* at 7:3).

Claims 15, 16, 18-25, 30, 31, 33, 34, 36, and 39-50 are pending and appealed. The claims stand rejected by the Examiner as follows:

1. Claims 15, 16, 18-25, 30, 31, 33, 34, 36, 39-46, and 49 under 35 U.S.C. § 103(a) as obvious in view of Depui et al. '184 (US 6,365,184 B1, issued Apr. 2, 2002) and Wurster (US 2,799,241, issued July 16, 1957) (Ans. 3).

2. Claims 15, 16, 18-25, 30, 31, 33, 34, 36, 39-46, and 49 under 35 U.S.C. § 103(a) as obvious in view of Depui et al. '771 (US 6,132,771, issued Oct. 17, 2000), Wurster, and Ohno et al. (US 4,017,647, issued Apr. 12, 1977) (Ans. 7).

3. Claims 15, 16, 18-25, 30, 31, 33, 34, 36, 39-46, and 49 under 35 U.S.C. § 103(a) as obvious in view of WO '624 (WO 96/01624, published Jan. 25, 1996), Wurster, and Ohno (Ans. 10);

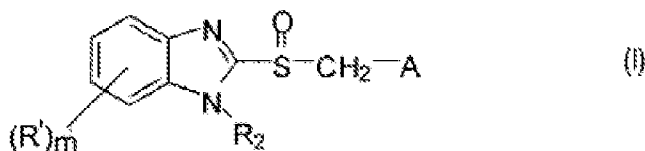
4. Claims 47, 48, and 50 under 35 U.S.C. § 103(a) as obvious in view of Depui '184, Wurster, Palomo Coll (US 5,232,706, issued Aug. 3, 1993), and Kim (US 5,219,870, issued Jun. 15, 1993) (Ans. 12); and

5. Claims 47, 48, and 50 under 35 U.S.C. § 103(a) as obvious in view of Depui '771 or WO '624; Ohno or Wurster; and Palomo Coll and Kim (Ans. 13-14).

Appellant argued the claims as a group and addressed the rejections collectively (Reply Br. 4). Therefore, we select claim 34 as representative for deciding all issues in this appeal. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Claim 34 reads as follows:

34. A process for making an oral pharmaceutical preparation comprising:
a) coating an inert nucleus to form a substantially non-porous layer thereon by spraying on the nucleus an aqueous or hydroalcoholic suspension-solution, which comprises:
(i) an active ingredient, said active ingredient consisting of a compound having anti-ulcer activity of general formula I:



wherein A is:



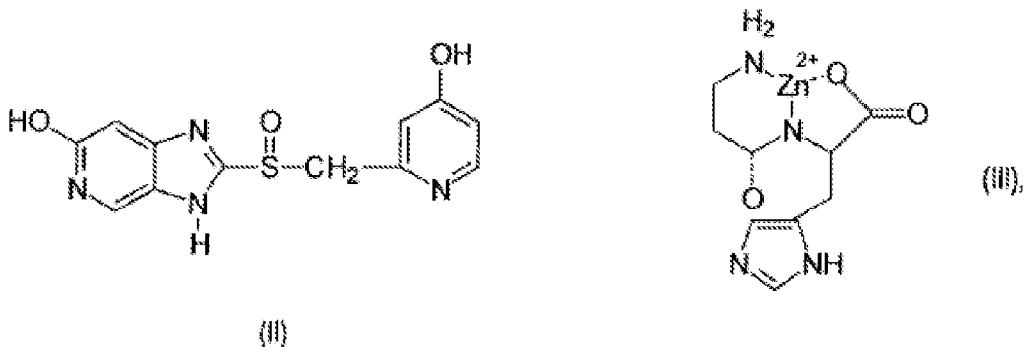
wherein R^3 and R^5 are the same or different, and may be hydrogen, alkyl, alkoxy, or alkoxyalkoxy;

R^4 is hydrogen, alkyl, alkoxy which can be fluorinated, alkoxyalkoxy, or optionally alkoxyalkoxy;

R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl;

R² is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl; and, m is a whole number from 0 to 4;

or of general formula II or III,



(ii) an alkaline reacting compound, and

(iii) at least one pharmaceutically acceptable excipient selected from the group consisting of: a binder, a surface-active agent, a filling material and a disintegrating-swelling excipient;

b) drying the active layer formed during said spraying to form a charged nucleus; and

c) coating the charged nucleus by spraying a solution which contains an enteric coating polymer with at least one pharmaceutically acceptable excipient to form a gastro-resistant external coating layer on said charged nucleus

wherein the steps a) to c) are performed in a Wurster-type fluidized bed coater.

THE SPECIFICATION

1.² According to the Specification, in “the present invention a formulation and a working methodology in a fluid bed of the ‘Wurster’ type or the like have been developed.” (Spec. 7:2-3).

2. The Specification describes a formulation comprising an anti-ulcer benzimidazole compound

² The numbered paragraphs used through this decision are findings of fact (“FF”).

with a homogenous active charge layer and a very unporous surface, formed by coating of an inert nucleus by spraying a single aqueous or hydroalcoholic mixture containing the active ingredient (anti-ulcer compound) together with the other excipients. Then, in the same equipment and following a short drying period, the granules obtained are subjected to a stage of enteric coating.

(Spec. 8:15-21.)

3.

The present invention satisfactorily resolves the difficulty involved in coating the inert nucleus with an aqueous or hydroalcoholic solution suspension containing . . . [an] anti-ulcer compound which is generally highly labile in an acid environment . . . and in aqueous dissolution, in the presence of disintegrating-swelling excipients which cause an increase of viscosity which enormously hinders spraying thereof onto the inert nuclei.

(Spec. 9: 5-9.)

4. “When a single suspension-solution is projected onto the inert nucleus, a less porous and more homogeneous product is obtained than in the procedures known to date, and all the subsequent operations are simplified considerably.” (Spec. 9:19-21.)

5. “Once the microgranules have been formed by spraying the aqueous or hydroalcoholic suspension-solution containing the active ingredient, they are dried and coated with a layer of the enteric coating.” (Spec. 14:4-6.)

6. Example 1 describes coating an inert nucleus with a solution comprising lansoprazole, disodium phosphate (alkaline compound), hydroxylpropyl-methyl cellulose, and other ingredients in a Wurster type fluid bed. (Spec. 18-19.) The granules are enteric coated (*id.* at 19).

7. The enteric coated pellets are described as stable and gastro-resistant over six months at two different temperatures (Spec. 20-21).

8. Example 2 shows similar results as in Example 1, but with a different proton pump inhibitor (omeprazole) (Spec. 22-25).
9. The Specification states that “[a]ll these results show the stability of the formulations object of the present invention, which moreover differ from those described in the prior art in that they have no intermediate separating layer between the active layer and the gastro-resistant layer.” (Spec. 25:6-8.)

CLAIM INTERPRETATION

Claim 34 is to a process of making an oral pharmaceutical preparation comprising three steps: a) coating an inert nucleus “to form a substantially non-porous layer” by spraying an aqueous or hydroalcoholic suspension-solution comprising one of a group of benzimidazole compounds; b) drying the active benzimidazole drug layer formed during the spraying to form a charged nucleus; and c) coating the charged nucleus with an enteric coating. The claim recites that “steps a) to c) are performed in a Wurster-type fluidized bed coater.”

The Examiner interpreted claim 34 not to exclude a separating layer between the active layer formed in step a) and the enteric coating of c) (Ans. 16). The Examiner reached this conclusion based on the “comprising” language recited in claim 34 (*id.*) and the interpretation that the recited “charged nucleus” of step b) could be understood to be formed from the active drug layer and a separating layer, rather than just the drug layer (*id.* at 18). The Examiner stated: “As it can be seen, the claims are not limited to coating the enteric coating *directly* to the charged nucleus. Thus, the claim

language does not exclude the separating layer. The claims merely state that the ‘charged nuclei’ [sic] is sprayed with an enteric coating.” (*Id.*)

During patent examination proceedings, claim terms are given “the broadest reasonable meaning . . . in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification.” *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). In this case, claim 34 recites that a solution comprising the formula I compound (the “drug layer”) is sprayed on an inert nucleus “to form a charged nucleus” and that the charged nucleus is coated by “spraying” it with enteric coating. The most natural interpretation of the words in the claim is that the enteric coating is applied directly to the drug layer. Consistently, the Specification does not state that a separating layer is utilized between the active layer and enteric coating. To the contrary, the Specification distinguishes the prior art by expressly stating that the resulting formulations “differ from those described in the prior art in that they have no intermediate separating later between the active layer and the gastro-resistant layer” (FF9). In view of the claim language and the Specification disclosure, persons of ordinary skill in the art would have understood that the claimed step c) in which the “charged nucleus” is coated with an enteric coating polymer means that the active layer is sprayed directly with the enteric polymer, without a separating or intermediate layer. Our interpretation is not reading limitations from the Specification into the claims, but rather interpreting step c) of claim 34 as a person would have understood it upon reading the Specification.

SCOPE AND CONTENT OF THE PRIOR ART

The Examiner relied on Depui '771, Depui '184, and WO '624 for their similar descriptions of producing an enteric coated oral dosage form comprising a proton pump inhibitor having a chemical formula that meets the general formula I recited in claim 34. There is no dispute the claimed "compound having anti-ulcer activity of general formula I" is described in the cited publications in an "oral pharmaceutical preparation." One of the main problems addressed in these publications is that benzimidazole compounds of the type recited in claim 34 are acid labile and degraded by contact with gastric juice (App. Br. 5). Enteric coatings are typically utilized in these formulations to protect the benzimidazole from premature degradation by the gastric juice (*id.*). However, the coatings interact with the benzimidazole core, leading to rapid degradation of the benzimidazole (*id.*). For this reason, a separating layer can be utilized between the benzimidazole and the enteric coating to protect the benzimidazole from coating-induced degradation.

Depui '771

10. Depui '771 states that it is "well known" that proton pump inhibitors are susceptible to degradation in acid media and "must be protected from contact with acidic gastric juice by an enteric coating layer" (Col. 2, ll. 46-53).

11. Depui '771 provides a tableted dosage form comprising individually enteric coating layered units, with each unit containing a proton pump inhibitor (col. 3, ll. 49-58). The units can be mixed with a prokinetic agent (*id.*).

12. The proton pump inhibitor can be layered on water insoluble or soluble seeds comprising oxides, celluloses, organic polymers, inorganic salts, and sugars (col. 8, ll. 46-62).
13. The inhibitor can be mixed with other components, including binders, surfactants, and alkaline substances (col. 8, l. 66 to col. 9, l. 42). Depui '771 states that the addition of an alkaline substance may further enhance the stability of the proton pump inhibitor (col. 12, ll. 59-62).
14. The seeds can be layered with the proton pump inhibitor by spray coating (col. 8, ll. 62-64).
15. "Before applying the enteric coating layer(s) onto the core material in the form of individual pellets or tablets, the pellets or tablets may optionally be covered with one or more separating layer(s)" (col. 9, ll. 46-50). "The separating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process." (Col. 9, ll. 57-61.)
16. "One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) using a suitable coating technique." (Col. 10, ll. 41-43.)
17. In Examples 1-14 of Depui '771, enteric coated dosage forms are described, each comprising a proton pump inhibitor (such as omeprazole or lanzoprazole) coated with a separating layer followed by the enteric coating layer.
18. Example 1 describes a process involving the following steps:

19. 1) spraying a mixture of magnesium omeprazole and hydroxypropyl methylcellulose in water on sugar sphere seeds in a fluid bed apparatus (col. 14, ll. 4-8 and 40-44);
20. 2) covering the coated seeds with a hydroxypropyl cellulose separating layer in a fluid bed apparatus (col. 14, ll. 45-46);
21. 3) in a fluid bed apparatus, spraying the layered seeds with an enteric coating (col. 14, ll. 47-51); and
22. 4) coating the enteric coating layered pellets with an over-coating and compressing into tablets (col. 14, ll. 55-62).

Depui '184

23. Appellants acknowledge that the disclosure of Depui '184 "is substantially similar to" Depui '771 "but the second active ingredient is a non-steroidal anti-inflammatory agent ('NSAID') in place of the prokinetic agent." (App. Br. 8.)
24. Example 4 of Depui '184 describes spraying lansoprazole (also known as lanzoprazole) onto inert cores in a fluid bed apparatus and then coating with sub-coating and enteric coating in a Wurster equipped fluid bed apparatus (col. 18, ll. 20-31). The Wurster equipped fluidized bed was also used in Example 6 of Depui '184 for coating the oral dosage form (col. 20, ll. 52-67).

WO '624

25. WO '624 describes a process similar to that in the Depui patents in which seeds sprayed and layered with a proton pump inhibitor, optionally mixed with alkaline compounds, are coated with an enteric coating layer,

optionally with a separating layer between the drug and enteric coating layers (1:16-18; 2:3-26; 13:5-12).

26. Example 11 of WO '624 is of a formulation comprising a core material containing a proton pump inhibitor, with no separating layer, and an enteric coating (28:15). The core material is produced as in Examples 1 and 10 (28:10). Example 1 is of a core material that comprises lansoprazole, hydroxypropyl methylcellulose, but no alkaline salt (19:10-17). Example 10 is of a core material that comprises pantoprazole, hydroxypropyl cellulose, but no alkaline salt (27:11-17).

Lovgren, U.S. Pat. No. 4,786,505 (Nov. 22, 1988) (cited by Appellant)

27. Lovgren states:

In order to obtain a pharmaceutical dosage form of omeprazole which prevents omeprazole from contact with acidic gastric juice, the cores must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, omeprazole rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discolored and lose in omeprazole content with the passage of time.

In order to enhance the storage stability the cores which contain omeprazole must also contain alkaline reacting constituents.

(Col. 1, ll. 48-59.)

28. To address this problem, Lovgren describes an enteric coated dosage form of omeprazole with a core “containing omeprazole mixed with alkaline compound or an alkaline salt of omeprazole” which is “coated with two or more layers”, at least one of these layers (the first or “separating” layer or “sub-coating”) separates the core from the enteric coating (the second layer).

(Col. 3, ll. 14-31; col. 4, ll. 3-45.)

29. Lovgren compares several different oral omeprazole dosage forms, including a formulation that lacks the separating layer (col. 6, ll. 55-65; formulation I as shown in Table 2 lacks an inner separating layer).

30. The formulation which lacked the inner separating layer exhibited rapid omeprazole degradation during storage for all the preparations, which additionally vary in the core formula. (Col. 7, ll. 12-30; Table 3, see entry for formula I; the color of the dosage form indicated its stability, with “A” meaning “white” which was indicative of high stability and “F” meaning “deep brown” and the lowest stability and most degradation.)

31. According to Lovgren, a magnesium compound in the inner separating layer had a “remarkable stabilizing effect” on degradation (col. 7, ll. 7-11).

32. Lovgren also determined the effect of a buffer salt on an enteric-coated omeprazole pellet “when the sub-coating is absent” (col. 12, ll. 40-44).

33. Based on these experiments, Lovgren concluded: “A high amount of buffer salt is needed in order to obtain a long shelf life for the product. At the same time this type of pellets shows inferior acid resistance properties.” (Col. 12, ll. 42-45.)

34. Example III, which is an enteric coated pellet with no sub-coating and 24 grams of a disodium hydrogen phosphate buffer salt, “retained” its original white color after storage for one month at 50°C (col. 14, ll. 33-38).

THE DECLARATIONS

Picornell, Molina, and Bravo (“PMB”) Declaration

35. The PMB declaration reproduced Example 6 of EP 0 642 797 (“EP”) (PMB Dec. 1-2) which lacked a sub-coating or separating layer.

36. The EP example used sugar spheres coated by spraying with lansoprazole, magnesium carbonate (an alkaline substance), and hydroxypropyl cellulose which were then coated with an enteric layer (PMB Dec. 2).

37. The declarants stated that Example 6 of the EP “does not yield lansoprazole granules suitable for subsequent enteric coating” (PMB Dec. 4).

38. The declarants stated that when they increased the binder material in the core, the granules were fragile, broke apart, and led to “degradation of the active ingredient as seen by the formation of a dark brown colouring” when contacted with the enteric coating (PMB Dec. 5).

39. The declarants also stated that the granule’s “resistance to gastric fluid” was “unacceptably low” (PMB Decl. 6).

Johansson Declaration

40. Ms. Johansson produced Example 5 of Depui ‘771, but omitted the separating layer which had been described as coating the core material (Johansson Dec. 1: ¶ 2; App. Br. 22).

41. Example 5 showed an oral dosage form with a core material comprising lansoprazole, but no alkaline salt (Johansson Dec. 1: ¶ 3).

42. According to Ms. Johansson, the enteric coated pellets produced without a separating layer showed a brownish color one hour after coating, indicating degradation of the lanzoprazole (Johansson Dec. 2-3).

43. In contrast, Ms. Johansson prepared pellets according to the instant application and found they remained stable during storage for several months (Johansson Dec. 3: ¶¶ 7-8).

Molina Declaration

44. Dr. Molina reproduced Example 11 of WO '624, which contained the core material of Examples 1 and 10 of WO '624, coated with an enteric coating layer but no separating layer. The core materials do not contain an alkaline or buffer salt (FF26).

45. According to Dr. Molina, the core material "had a white-creamy color prior to the application of the enteric coating layer" but "serious problems were encountered" when applying the enteric coating because the pellets "showed an increasing tendency to stick" and they "began to exhibit a brown color" as "a consequence of" rapid degradation" (Molina Dec. ¶¶ 10-13 & 16).

STATEMENT OF THE ISSUES

The Examiner took the position that Depui '771, Depui '184, and WO '624 described a process that met all three steps of claim 34, but did not explicitly teach that each of the steps was carried out in a Wurster fluidized bed apparatus as recited in the claim. The Examiner acknowledged that the cited prior art described a separating layer in their formulation between the active and enteric coatings, but noted that it was taught in the prior art as

optional. The Examiner also found that Depui '184 taught using a Wurster equipped fluidized bed apparatus for preparing the sub- and enteric coatings (FF24) and concluded that based on this disclosure and that of Ohno, it would have been obvious to use the Wurster bed for the proton pump inhibitor coating, as well (Ans. 6).

Appellant takes the position that the Examiner erred in finding the claimed subject matter obvious. We summarize the main errors alleged by Appellant as follows:

Appellant contends that there is no prima facie case of obviousness because the cited references do not enable how to make a stable oral formulation.

Appellant contends that based on the prior art teachings, including that of Lovgren, persons of ordinary skill in the art would not have been prompted to make a formulation without a separating layer since it would have been believed to be unstable.

Appellant also contends that the neither the Depui patents nor WO '624 teach a non-porous coating as recited in claim 34.

Appellant provided Declarations and other evidence which he asserts establish a lack of prima facie obviousness and demonstrate unexpectedly improved results (Reply Br. 15). Appellant contends that the Examiner dismissed the evidence and did not properly reconsider the rejection in view of the Declarations and the Lovgren patent (App. Br. 19).

ANALYSIS

Appellant contends that a prima facie obviousness case has not been made since persons of ordinary skill in the art would not have been

prompted to have produced an oral pharmaceutical preparation comprising an active benzimidazole layer on an inert nucleus, coated directly with an enteric polymer, and which lacks a separating layer between the active layer and enteric coating. As evidence of this, Appellant cited:

1) Prior art teachings from Lovgren and the Depui patents that proton pump inhibitors, such as the benzimidazole omeprazole, were rapidly decomposed by acid components from the enteric coatings, necessitating a separating layer between the active benzimidazole layer and the enteric coating (FF10-24, 27-34);

2) Declarations by PBM, Johansson, and Molina that, when oral enteric coated benzimidazole formulations in the prior art were reproduced without a separating layer, the resulting products were unstable and rapidly degraded, in contrast to formulations produced according to the claimed method (FF35-45).

Based on this evidence, Appellant argues that persons of ordinary skill would not have found Depui's suggestion that the separating layer is optional to be credible nor could the ordinarily skilled worker have produced a stable benzimidazole composition without a separating layer.

When assessing patentability, the PTO must consider all evidence of nonobviousness. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

As to the Lovgren patent, we acknowledge that clear statements, consistent with those in the Depui patents, were made that benzimidazole compounds were susceptible to degradation by the acidic enteric coating unless protected, preferably by a separating layer. Lovgren performed experiments which showed that in the absence of a separating layer, the benzimidazole formulation rapidly degraded (FF29-31). Based on this

disclosure, Appellant concluded that the Depui statements about the separating layer being “optional” would not have been considered to be a credible suggestion to be followed.

The entirety of the evidence does not support this argument. First, it should be noted that in spite of Lovgren’s evidence (FF29-31), both Depui patents still chose to describe the separating layer as optional, even though there were specific formulations in which omission of the separating layer had been shown to be unsuitable. Secondly, WO ‘624 had an explicit example of a formulation comprising an enteric coated benzimidazole with no separating layer (FF26), giving further credence to Depui’s statement that the separating layer is optional. With an actual example described in the prior art, it is more likely that the Depui’s statements that the separating layer could be omitted were believable – since there is prior art which did just that.

Secondly, when the Lovgren patent is read in its entirety, it is apparent that its full disclosure is not as black and white as Appellant would have it. At columns 12-14, Lovgren describes comparative examples in which a separating layer is omitted (FF32-34). In these examples, Lovgren reports that even when the separation layer is omitted, degradation of the benzimidazole omeprazole could be avoided by including a high amount of an alkaline buffer salt in the omeprazole core (FF32-34). Thus, Lovgren showed how to avoid acid degradation when the separating layer is omitted.

The sum of the testimonial evidence also does not support Appellant’s argument. Our reasoning is explained in more detail below.

The core materials reproduced in the Johansson and Molina declarations do not comprise an alkaline or buffer salt (FF26, 41, & 44).

According to Lovgren, when the sub-coating is absent, a “high amount of buffer salt is needed in order to obtain a long shelf life for the product” (FF33). Therefore, based on Lovgren, it would have been expected that the examples reproduced by Ms. Johansson and Dr. Molina – without the buffer salt – would have been expected to show rapid degradation as they did. *See also* Depui ‘771 (FF13).

The PBM declaration utilized a core material with lansoprazole and magnesium carbonate, an alkaline salt, as in the EP publication (FF37). The declarants stated that the granules were not suitable for enteric coating, broke apart, and that the lansoprazole rapidly degraded when in contact with the enteric coating (FF37-38). Based on the failure of this example, Appellant argued that the claimed method would not have been obvious over the Depui patents and WO ‘624.

The evidence in the PBM declaration is not persuasive. As admitted by Appellant, the EP omitted information on how its granules were produced (PBM Dec. 2-3). On the other hand, Lovgren described conditions to successfully coat benzimidazole cores with enteric polymers and preserve the benzimidazole stability (FF32-34). Therefore, the failure of the EP example to produce stable granules that could be coated with an enteric polymer can be attributed to its lack of a complete manufacture description, rather than a general inability to produce stable benzimidazole formulations without a separation layer. *See also* Ans. 22.

Appellant also argued that the cited references do not describe how to make a seed coated with a substantially non-porous active layer and the Examiner has not provided sufficient evidence that the active layer in the prior art was non-porous (App. Br. 12).

The PTO does not have the ability “to manufacture products or to obtain and compare prior art products.” *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). Thus, once “the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990).

In this case, the Depui ‘771 example (FF19) and the WO ‘624 example (FF26) utilize hydroxypropyl methylcellulose and hydroxypropyl cellulose in their core materials, the same type of material in Examples 1 and 2 of the Specification (Spec. 18 and 22). Based on this chemical similarity, the Examiner reasonably believed that they would form a non-porous coating as recited in the claim. The burden properly shifted to Appellant to show that the prior art materials did not form a non-porous layer as claimed. Appellant has not provided evidence to the contrary.

Appellant challenges the Examiner’s finding that Ohno taught the equivalence of a list of coating devices that included the Wurster-type fluidizing coater (App. Br. 15).

Ohno explicitly states that “[a]ny conventional coating machines” can be employed in its method (Ohno, at col. 3, ll. 24-26). Based on this teaching, the Examiner found the persons of ordinary skill in the art would have been motivated to use a Wurster-type apparatus “since Ohno teaches that the Wurster-type apparatus among other fluid bed coaters are known and conventionally utilized in the art for coating purposes and all the coating machines work under the same principle.” (Ans. 9.) We agree with the Examiner that Ohno’s teaching, combined with Depui ‘184 in which a Wurster-type apparatus was actually used (FF24), would have made it

obvious to have tried the Wurster apparatus as it was a recognized conventional coating machine that would have been expected to work.

Unexpected results

Next, we move to the question of whether Appellant has established unexpected results for the full scope of the claim. The Specification provides two examples of benzimidazole formulations, prepared using a Wurster type fluid bed, each formulation which lacked a separating layer. Both of the formulations were shown to be stable for a long storage time and to possess high gastro-resistance. (Spec. 20 & 24-25.)

- The Example 1 active layer comprised lansoprazole, sodium lauryl sulphate, disodium phosphate buffer salt, lactose, hydroxypropylmethyl cellulose, and hydroxypropyl cellulose. (Spec. 18.)

- The Example 2 active layer comprised omeprazole, sodium lauryl sulphate, disodium phosphate buffer salt, lactose, hydroxypropylmethyl cellulose, and hydroxypropyl cellulose. (Spec. 22.)

Appellant states that “the pellets of the present invention had improved stability and are stable for many months which would be an unexpected improvement over the prior art pellets with a chemical stability of an hour.” (Reply Br. 13.)

To establish unexpected results, the claimed subject matter must be compared with the closest prior art. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). Appellant has not established that the prior art to which Examples 1 and 2 have been compared is the closest. For example, in the Johansson and Molina Declarations, Appellant compared certain Depui ‘771 and WO ‘624 examples which lack the alkaline salt (FF41, 44) to

formulations prepared in accordance with the Specification. The Lovgren example in which the sub-coating was omitted appears to be closer, and in these formulations, Lovgren taught the addition of a high content of a buffer salt resulted in a long storage period (FF32-34) – the same result reported in Examples 1 and 2 of the Specification. Appellant did not explain why examples lacking alkaline substance were compared to the examples in the Specification comprising the alkaline substance, when both Depui ‘771 (FF13) and Lovgren teach that an alkaline substance enhances stability.

As to the difference in gastro-resistance between the formulation of Lovgren’s example and those in the Specification, Appellant has not provided evidence, or even stated, that the improvement was substantial and unexpected. “Mere improvement in properties does not always suffice to show unexpected results. . . . [H]owever, when an applicant demonstrates *substantially* improved results, . . . , and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary.” *In re Soni*, 54 F.3d at 751.

The PMB Declaration reproduced an example with an alkaline substance, magnesium carbonate, and a benzimidazole compound (FF36). Again, Appellant has not explained why this example is the closest prior art, rather than the examples in the Lovgren, WO ‘624, and Depui patents. For instance, the reproduced example utilized magnesium carbonate as the alkaline substance, while Examples 1 and 2 in the Specification used a disodium phosphate, as did Lovgren (FF34). Finally, the PBM declarants did not state that their results were substantial and unexpected improvements nor does it appear that Appellant intended to rely on this declaration for unexpected results (App. Br. 22).

Unexpected results must be “commensurate in scope with the degree of protection sought by the claimed subject matter.” *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005). In response to the Examiner’s finding that the claimed improvement is not commensurate in scope with the claim, Appellant states hydroxypropyl cellulose was present in Lovgren’s preparations of Tables 1, 2, and 3, but did not provide protection unless a separating layer was present. Therefore, they argue that it was the separating layer which was effective, not the materials in the core that produced the stability. (Reply Br. 14-15.)

This argument is not persuasive. Claim 34 is open-ended as to the alkaline reacting compound, binder, surface-active agent, filling material and disintegrating excipient. However, Examples 1 and 2 of the Specification each have the same components in approximately the same amounts. As shown by Lovgren, at least the amount of alkaline reacting compound in the core material influences the storage characteristics. Appellant has not provided evidence that the observed improvement in stability and gastro-resistance would be associated with other components (different binder, different surface-active agent, etc.) or the same components in different amounts. Appellant also has not provided evidence that the Wurster fluid bed is responsible for the enhanced stability and confers stability to all compositions produced by the claimed process.

As to Appellant’s argument that Lovgren shows that the core material does not affect stability, we find that the prior art as a whole does not support this position. Depui ‘771 states that an alkaline substance combined with a proton pump inhibitor in the active layer can enhance the latter’s stability (FF12-13). This statement is echoed in Lovgren (FF27, 31-34).

In sum, the totality of the evidence supports the Examiner's conclusion that the subject matter of claim 34 would have been obvious to persons of ordinary skill in the art at the time the application was filed.

CONCLUSION OF LAW

The Examiner did not err in finding that the subject matter claim 34 would have been obvious to a person of ordinary skill in the art at the time the application was filed in view of Depui '184, Depui '771, WO '624, Wurster, Ohno (*see* Rejections 1-3 listed on page 2 *supra*), Lovgren, and the Declarations of PBM, Johannson, and Molina.

SUMMARY

The obviousness rejections of claims 15, 16, 18-25, 30, 31, 33, 34, 36, and 39-50 are affirmed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

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